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A case-referent study of lung cancer, occupational exposures and smoking

II Role of asbestos exposure

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KJUUS H, SKJÆRVEN R, LANGÅRD S, LIEN JT, AAMODT T. A case-referent study of lung cancer, occupational exposures and smoking: II Role of asbestos exposure. *Scand J Work Environ Health* 12 (1986) 203—209. In a hospital-based case-referent study of 176 incident lung cancer cases, ascertained during a five-year period from two county hospitals, the role of asbestos exposure and smoking has been studied. Information on asbestos exposure was obtained from personal interviews, and allocated to four exposure categories, according to the intensity and duration of the exposure. Twenty-five percent of the cases and 10 % of the referents had been moderately to heavily exposed to asbestos during their working career. A statistically significant trend in risk ratio related to the degree of exposure was observed, with a more than fourfold risk among the heavily exposed. The strongest association was found between asbestos exposure and small cell carcinoma, and the weakest association between asbestos exposure and adenocarcinoma. Very high risk ratios were observed among asbestos-exposed subjects who were heavy smokers, and the interaction observed between asbestos and smoking conformed more closely to a multiplicative model than to an additive one. The results suggest that the observed association between lung cancer and occupational exposures in this study was, to a large extent, due to asbestos exposure. Information on such exposure was missing in 90 % of the medical records of these patients.

Key terms: histology, interaction, medical records, personal interviews.

Much attention was paid to the observation of lung cancer risk in different asbestos-exposed cohorts in the 1970s. In the last few years, interest has changed in the direction of the total disease-producing role of asbestos exposure in the general population. Several population estimates of the role of asbestos exposure for present and future lung cancer mortality have recently been presented (5, 7, 22, 31), and asbestos exposure has been suggested as the most important single factor contributing to occupational lung cancer (7, 8).

As the number of persons occupationally exposed to asbestos in a population is seldom known, most population estimates presented are based upon indirect measures, extrapolated from known exposure-disease associations in highly exposed workers such as asbestos miners, insulators, and shipyard workers (5, 7). Population-based studies might have provided more direct information on the disease-producing role of the total asbestos exposure in the general population. However, detailed asbestos exposure is seldom available in such studies, based as they often are upon register data, eg, death certificates and cancer registers. The use of an occupation and exposure linkage system, in which potential asbestos exposure is based upon job title information (14), represents an improvement, but is still a crude measure of the real exposure. Thus a complete exposure history is of particular importance in situations where the asbestos exposure occurs in limited periods, is not reflected by the occupational title, or occurs in occupations not traditionally associated with asbestos exposure. Personal interviews seem therefore to be the most sensitive source for the direct characterization of asbestos exposure in the general population.

On the basis of detailed information of asbestos exposure obtained from personal interviews and questionnaires, we have studied the relationship between asbestos exposure and lung cancer in a case-referent study of 176 male cases and 176 referents, recruited from two county hospitals in southeast Norway. Some other aspects of this study have been subject to separate presentations (18, 19).

Subjects and methods

The main design of the study has been presented in another paper (19). A detailed asbestos history was obtained through personal interview and a questionnaire, from 176 male lung cancer cases [International Clas-

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sification of Diseases (ICD) 162, 163] and 176 referents, recruited during the five-year period 1979—1983 from the medical wards of Telemark County Hospital and Vestfold County Hospital. The questionnaire covered questions on the first year of exposure and number of years exposed, together with the duration and intensity of the asbestos exposure in each particular job held in a lifetime. Potential environmental asbestos exposure of nonoccupational origin was not taken into account. The asbestos history of each participant was classified according to five levels of intensity of exposure (no exposure, uncertain, light/indirect, moderate, and heavy) and duration of exposure in number of years. Asbestos exposure for more than 10 d/month counted as full-time, 5—9 d/month as half-time, 1—4 d/month as one-fifth of the time, and exposure with a duration of less than 1 d/month counted as one-tenth of the years exposed. These two measures were combined, and the asbestos exposure of each subject was allocated to one of four grades, shown in table 1. This classification was performed blind as to the case-referent status of the subject, and it was done after all the patient interviews had been finished. Indirect occupational exposure through fellow workers' handling of asbestos, and, eg, garage work with sporadic repair of brake linings was usually allocated to grade 1. The participants were also allocated to the main occupation/industry in which the most relevant asbestos exposure had taken place. Further design matters, including the general procedure for the exposure assessment, have been dealt with elsewhere (19). In a sample of 40 cases and 40 referents we have also studied to what degree information on asbestos exposure was available in the medical records of the patients.

In an examination of the combined effect of smoking and asbestos exposure, smoking was classified into three to five levels, based upon lifetime consumption of tobacco, in grams. This cumulative dose was redefined to the number of cigarettes smoked per day, on the assumption of a smoking time of 45 years, which was the average smoking time among the smokers.

The data have been analyzed by a dual approach, where the odds ratios have been used as estimators of risk ratio (RR). The main analyses were performed with an unconditional logistic regression modeling technique. In addition, a stratified analysis was performed to evaluate the combined effect of smoking and asbestos exposure. Independence of the separate factors was based upon additivity of the risk differences (RD = RR − 1), and Rothman's index of interaction was calculated as a quantitative measure of interaction (26). The estimation of 95 % confidence intervals was based upon the estimat errors from the regressi

Table 1. Assessment of asbestos exposure.

Grade	Assessment
0	No exposure
1	Uncertain, indirect, light/sporadic exposure
2	Moderate exposure for more than one year but less than 10 years or heavy exposure for less than one year
3	Moderate exposure for 10 years or more or heavy exposure for one year or more

Table 2. Risk ratio (RR)[a] for lung cancer according to asbestos exposure (grades 0—3 as presented in table 1), by hospital, adjusted for smoking and urban/rural status.

Hospital	Asbestos grade				Total
	0	1	2	3	
Telemark					
Cases	56	48	17	15	136
Referents	79	44	9	4	136
RR, adjusted 2	1.0	1.2	2.7	4.3	.
Vestfold					
Cases	15	13	6	6	40
Referents	23	13	2	2	40
RR, adjusted 2	1.0	2.4	2.6	5.3	.
Total					
Cases	71	61	23	21	176
Referents	102	57	11	6	176
RR, unadjusted	1.0	1.5	3.0	5.0	.
RR, adjusted 1	1.0	1.5	3.1	4.6	.
RR, adjusted 2	1.0	1.4	2.8	4.3	.
RR, adjusted 3	1.0	1.2	2.7	4.1	.
RR, adjusted 4	1.0	1.3	3.6	4.0	.
95 % confidence interval for RR, adjusted 2	.	0.8—2.3	1.2—6.7	1.5—12.0	.

[a] Adjusted 1 = smoking, three levels (0—9, 10—19, ≥20 cigarettes/d).
Adjusted 2 = smoking, three levels (0—9, 10—19, ≥20 cigarettes/d) and urban/rural status.
Adjusted 3 = smoking, five levels (0—4, 5—9, 10—19, 20—29, ≥30 cigarettes/d) and urban/rural status.
Adjusted 4 = smoking, linear adjustment.

Test for trend: G = 12.2, 3 df, p = 0.007.

Test for departure from linearity: ΔG = 0.47, 2 df, p = 0.80.

Table 3. Risk ratio (RR)[a] f as presented in table 1). T

Histology	
Squamous cell carcinoma	
Small cell carcinoma	
Adenocarcinoma	
All types	

[a] Adjusted for smoking, th

Results

The distribution of lun from the two hospitals a (grade 0—3) is shown in cases (N = 105) and 42 had experienced some bestos during their wor cancer patients (25 %) been moderately to heav year (grade 2—3). The exposed subjects was fa pitals, both for the case was a statistically signific cancer related to the degr hood ratio (G) = 12.2, p = 0.007], with a mor those in the highest expo to be linear in the logi p = 0.80). Only small c mates were observed wh for smoking at differ between lung cancer and found in the age group ately exposed subjects ca and heavily exposed subj for lung cancer.

Due to the sparse nun each cell when the mate several of the associatio dichotomous scale of as versus grade 0—1). Wit types of lung cancer, t found between small cel posure (RR = 3.0), and adenocarcinoma and as (table 3). There were fo cases, of which three exposed grade 2 and 3. O was a fisherman, spora

Table 3. Risk ratio (RR)[a] for histological subgroups of lung cancer, according to asbestos exposure (grades 0—1 and 2—3 as presented in table 1). Total reference group used for each histological subgroup.

Histology	Number of cases	Asbestos exposure						95 % confidence interval
		Grade 0—1			Grade 2—3			
		Cases (N)	Referents (N)	RR	Cases (N)	Referents (N)	RR	
Squamous cell carcinoma	94	74	159	1.0	20	17	2.7	1.2—6.1
Small cell carcinoma	38	28	159	1.0	10	17	3.0	1.1—8.1
Adenocarcinoma	21	17	159	1.0	4	17	2.2	0.6—8.2
All types	176	132	159	1.0	44	17	2.9	1.5—5.8

[a] Adjusted for smoking, three levels (0—9, 10—19, ≥20 cigarettes/d) and urban/rural status.

based upon the estimated coefficients and standard errors from the regression model.

Results

The distribution of lung cancer cases and referents from the two hospitals according to asbestos exposure (grade 0—3) is shown in table 2. Sixty percent of the cases (N = 105) and 42 % of the referents (N = 76) had experienced some exposure (grade 1—3) to asbestos during their working career. Forty-four lung cancer patients (25 %) and 17 referents (10 %) had been moderately to heavily exposed for more than one year (grade 2—3). The distribution of the asbestos-exposed subjects was fairly similar for the two hospitals, both for the cases and for the referents. There was a statistically significant trend in risk ratio for lung cancer related to the degree of asbestos exposure [likelihood ratio (G) = 12.2, 3 degrees of freedom (df), p = 0.007], with a more than fourfold risk among those in the highest exposure group. The trend seemed to be linear in the logistic scale (ΔG = 0.47, 2 df, p = 0.80). Only small changes in the risk ratio estimates were observed when the estimates were adjusted for smoking at different levels. The association between lung cancer and asbestos exposure was mainly found in the age group 60—69 years, where moderately exposed subjects carried a threefold increased risk and heavily exposed subjects an eightfold increased risk for lung cancer.

Due to the sparse number of cases and referents in each cell when the material was subdivided further, several of the associations studied were based upon a dichotomous scale of asbestos exposure (grade 2—3 versus grade 0—1). With regard to the histological types of lung cancer, the strongest association was found between small cell carcinoma and asbestos exposure (RR = 3.0), and the weakest association for adenocarcinoma and asbestos exposure (RR = 2.2) (table 3). There were four mesotheliomas among the cases, of which three were classified as asbestos-exposed grade 2 and 3. One patient with mesothelioma was a fisherman, sporadically exposed to asbestos during the semiannual maintenance of the motor in his fishing boat, classified as grade 1 (17).

Table 4. Distribution of cases and referents according to asbestos exposure and the main occupation/industry in which the asbestos exposure (grade 2—3) took place.

Asbestos exposure	Cases (N)	Referents (N)	Odds ratio
Not exposed (grade 0)	71	102	.
Exposed (grade 2—3)			
Electrochemical process work	8	6	1.9
Electrochemical maintenance work	12	2	8.6
Shipbuilding	10	2	7.2
Ship engine maintenance work	5	1	7.2
Engineering workshop	2	2	.
Smelting/foundry work	1	2	.
Plumber	—	1	.
Carpenter	—	1	.
Electrician	2	—	.
Other	4	—	.

The odds ratio for lung cancer among those with moderate or heavy asbestos exposure was highest for maintenance workers in the electrochemical industry (RR = 8.6) and for shipyard workers and ship engine maintenance workers (RR = 7.2) (table 4).

On the basis of the risk differences from the stratified analysis (table 5), asbestos-exposed (grade 2—3) subjects who were moderate smokers (10—19 cigarettes/d) had a relative excess risk of 16.9, whereas 3.1 + 1.4 = 4.5 would be expected if the two causes were additive. Similarly, asbestos-exposed persons who were heavy smokers (>20 cigarettes/d) carried a relative excess risk of 28.8, whereas 13.5 + 1.4 = 14.9 would be expected for independent causes. The point estimate of the index of interaction was 16.9/4.5 = 3.8 and 28.8/14.9 = 1.9 for the two smoking levels, a result indicating that the combined effect is two to four times higher than what would be expected if the causes acted independently.

If the multiplication of the risk ratios were used as the criterion for interaction assessment, the expected risk ratio of asbestos and moderate smoking would be 9.8, which is lower than the observed risk ratio of 17.9. If a multiplicative effect of heavy smoking and asbestos exposure is assumed, the expected risk ratio would be 34.8, which is somewhat higher than the observed value of 29.8.

Table 5. Assessment of the combined effect of asbestos exposure and smoking. Comparison of stratified analysis and logistic regression (log regr) analysis. (RR = risk ratio)

Asbestos exposure[a]	Cases (N)	Referents (N)	Stratified		Log regr RR[b]	Index of interaction (point estimate)
			RR	RR−1		
Grade 0—1						
0— 9 cigarettes/d	29	96	1.0	0	1.0	.
10—19 cigarettes/d	68	55	4.1	3.1	4.4	.
≥20 cigarettes/d	35	8	14.5	13.5	14.2	.
Grade 2—3						
0— 9 cigarettes/d	8	11	2.4	1.4	2.9	.
10—19 cigarettes/d	27	5	17.9	16.9	12.8	3.8
≥20 cigarettes/d	9	1	29.8	28.8	41.2	1.9

[a] See table 1 for an explanation of the different grades of exposure.
[b] Adjusted for urban/rural status.

Table 6. Risk ratio[a] for lung cancer for combined exposure to asbestos (four levels) and smoking (five levels).

Cigarettes/d	Asbestos grade[b]			
	0	1	2	3
0— 4	1.0	1.2	2.7	4.1
5— 9	2.9	3.5	7.8	11.9
10—19	9.1	10.9	24.6	37.3
20—29	16.5	19.8	44.6	67.7
≥30	90.3	108.4	243.8	370.2

[a] Adjusted for urban/rural status.
[b] See table 1 for an explanation of the grades of exposure.

Table 7. Risk ratio (RR) for lung cancer according to exposure status of occupational titles, adjusted for asbestos exposure. (95 % CI = 95 % confidence interval)

	Adjusted risk ratio			
	Smoking[a] and urban/rural status		Smoking[a], urban/rural status and asbestos[b]	
	RR	95 % CI	RR	95 % CI
Main occupation:				
No exposure (OT−)	1.0	.	1.0	.
Possible exposure (OT?)	1.7	0.9—3.0	1.6	0.9—2.8
Definite exposure (OT+)	2.3	1.3—4.2	1.9	1.0—3.4
Number of years with definite exposure (OT+)				
—	1.0	.	1.0	.
1— 9	1.3	0.7—2.7	1.3	0.7—2.6
10—19	2.2	1.1—4.3	1.8	0.9—3.6
20—29	2.2	1.1—4.4	1.8	0.8—4.3
≥30	3.8	1.6—8.9	3.0	1.2—7.2

[a] Three levels (0—9, 10—19, ≥20 cigarettes/d).
[b] Two levels (grade 0—1, 2—3).

When asbestos exposure and smoking were further subdivided into four and five levels, respectively, very high risk ratios were observed for the combination of heavy smoking and heavy asbestos exposure (table 6).

In another part of this study a statistically significant association between lung cancer and occupational title-based indices was shown (19) when exposure status of main lifetime occupation and number of years in exposed occupations were used as the exposure variables. When the risk ratios for these associations were adjusted for asbestos exposure, several estimates were reduced to a nonsignificant level (table 7).

When information on asbestos exposure was searched for in the medical records of the 40 lung cancer cases from Vestfold County Hospital, only four of the records provided such information. Three of the cases had relevant asbestos exposure, while one patient was unexposed. No information on asbestos exposure was available in the medical records of the referents. This situation contrasted with that provided by the interview, which revealed moderate to heavy exposure (grade 2—3) among 30 % of the cases and 10 % of the referents.

Discussion

When different sources of exposure data are considered, interview data seem to be unique in providing detailed information on both occupational and non-occupational exposures. In spite of the obvious advantages in obtaining exposure information by personal interviews, the validity of this method for exposure characterization is also threatened in several ways (21, 27). The problem of recall bias seems to be the most important, although occupational data seem to be less influenced by general memory loss or selective recall than data from other fields of epidemiology (3, 11, 25). With the use of hospital referents, the information obtained from the cases and the referents might be more comparable than if population-based referents were used (6). Even so, the possibility of an exaggeration of the asbestos exposure among the cases cannot be ruled out. The increased public awareness of claims for compensation due to asbestos-related diseases in Norway might be particularly worrying in this respect. However, this phenomenon was only just beginning in 1983, at the end of the study period. Furthermore, the majority of the cases did not know that they had lung cancer at the time of the interview. In addition, the asbestos classification was undertaken not only on the basis of the questionnaire data, but also to a large extent upon the general occupational history, where the interviewer had acquired, from previous surveys,

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The problem of recall bias might also be evaluated retrospectively. Axelson has suggested that, if the subjects within a given occupational category have made exaggerated claims about their exposure, fewer cases should appear among the unexposed in that job category (2). One of the occupational groups in which asbestos is commonly used is metal workers (code 75), and we have evaluated the asbestos exposure among them. There was no indication of a preventive effect among the unexposed metal workers, and this result suggests that no serious recall bias was operating in the present study with regard to potential overestimation of asbestos exposure among the cases.

As the medical condition for which the referents were admitted to the hospital can hardly be seen to be positively or negatively associated with previous asbestos exposure, the exposure frequency among the referents might be used as a reflection of the asbestos exposure in the study area (6). However, the prevalence of "asbestos exposure" in a population is, to a high degree, dependent upon the definition of the exposure and the source of information for the exposure estimation. Not surprisingly, therefore, very different population-based estimates of asbestos exposure have been presented (5, 7, 12, 22, 31).

In a recently performed population-based survey of asbestos exposure among 21 000 men 40 years of age or more in Telemark, 18 % stated some degree of asbestos exposure in a self-administered questionnaire (B Hilt, personal communication). This figure is considerably lower than the figure of 42 % obtained from the detailed interviews of the present study, which also, however, included subjects with uncertain and indirect exposure (grade 1).

When using a self-administered questionnaire among lung cancer patients, Hillerdal and co-workers (12) found that 35.8 % were occupationally exposed to asbestos, while Pastorino et al (24) reported asbestos-exposure among 28 % of their male lung cancer cases from an industrialized area in northern Italy. Together with the 25 % definitely exposed (grade 2—3) and 35 % possibly/sporadically exposed (grade 1) lung cancer cases in the present study, these results underline the public health importance of asbestos exposure in the development of lung cancer among men.

We knew beforehand of several large electrochemical plants in Telemark where asbestos had been in regular use in previous years and therefore were aware that the study was being performed in an area with a potentially high exposure prevalence and that the external validity of the study might therefore be low. The finding of a corresponding prevalence of asbestos exposure among the subjects from Vestfold County, which is considered a moderately industrialized county, suggests that the results from the present study might also be relevant outside the study area.

The majority of the asbestos-exposed subjects in our study had their main exposure during the 1950s. This occurrence may partly explain the fact that the excess lung cancer risk was mainly confined to the 60- to 65-year age group. A declining risk among old subjects has also been observed by others (29, 30). When adjusted for smoking (five levels) and urban/rural status, the risk ratio for indirect or light/sporadic asbestos exposure (grade 1) was not significantly elevated in the present study (RR = 1.2). The high risk ratios found for electrochemical maintenance work and shipbuilding are in accordance with those from previous reports (4, 13, 22).

With regard to the histological pattern of asbestos-related lung tumors, Whitwell et al (33) reported a fairly high percentage of adenocarcinoma (34 %) among workers suffering from asbestosis. Kannerstein & Churg (15) and Hillerdal et al (12) found no essential difference between exposed and unexposed lung cancer patients, while Auerbach and co-workers (1) reported an excess of small cell carcinoma among asbestos-exposed subjects. In spite of the low numbers, the present study indicates a stronger relationship between asbestos and Kreyberg type I tumors (small cell carcinoma and squamous cell carcinoma) than for asbestos and type II tumors (adenocarcinoma) (20). One might further discuss whether or not mesotheliomas should be included in this material of lung cancer patients. Being a separate histopathological tumor of the pleura, strongly associated with asbestos, but not shown to be associated with smoking, mesotheliomas have little in common with other tumors of the lung. However, from a public health point of view, the total burden of asbestos-related tumors of the respiratory system would be of primary interest, and the cases were therefore included in the study.

The logistic regression method used in the present study implies a multiplicative statistical relationship between the effects of the study exposures included in the model. Although previous studies of the combined effect of asbestos and smoking might justify such a model (10, 28), the quantitated relationship between factors seldom conform perfectly to a chosen model (23). An additional stratified analysis was therefore performed for tentative quantification of the interaction between the two factors in the present data. However, this evaluation was hampered by the sparse number of subjects, in particular in the unexposed categories, which led to the use of a dichotomous asbestos variable (grade 2—3/0—1) and an "unclean" reference category for smoking (0—9 cigarettes/d). Even by this dilution of the unexposed categories, the stratified analysis suggests that the synergism observed between asbestos and smoking in this study more likely conforms to a multiplicative model than to an additive one. The study also demonstrates that the quantitative relationship observed between these factors is to a high degree dependent upon the chosen scale for

categorization of the study variables, and in particular of the definition of the unexposed category (24, 32).

Several of the associations observed in another part of this study between lung cancer and study variables based upon occupational title (19) became statistically nonsignificant when adjusted for a dichotomized asbestos variable (grade 2—3/0—1) (table 7). Together with the observed high prevalence of asbestos exposure among the subjects in this study, the results support the assumption that asbestos is one of the major factors contributing to occupational lung cancer in the study area. By contrast, less than 1 % of the 950 lung cancers occurring annually among men in 1978—1982 in Norway were notified to the Social Security Office as being due to asbestos.

Since 1985 the installation of new asbestos products has been generally prohibited in Norway, and all handling of old asbestos is subject to strong safety measures. The primary prevention of asbestos-related diseases in this country should therefore be progressing satisfactorily. However, serious health consequences of the asbestos exposure occurring between 1950 and 1980 will still be with us for several decades, and it is important that these conditions be identified. Clinicians may play an important role in the detection of these conditions (9), and detailed information on asbestos exposure should therefore be available in the medical record of all lung cancer patients.

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